REMARKS

The Office Action dated December 17, 2003, has been received and reviewed. Claims 1-7 and 11 are under examination in this application. The Examiner has withdrawn Claims 8-10 and 12-32 from consideration. Claim 33-34 has been added. Applicants have indicated these claims as withdrawn in view of the response to the restriction requirement. Applicants respectfully request reconsideration of the application as amended herein and in view of the arguments below. Additionally, Applicants confirm their election of Claims 1-7 and 11 in response to the restriction requirement.

I. Claim Amendments

Claim 1 has been amend to include the recitations of Claim 3 so that Claim 1 includes the sequence identifier for the amino acid sequence. Additionally, Applicants have amended Claim 1 to recite 85% homology rather than the hybridization language. Support for this amendment may be found on page 12, lines 29-32. Applicants have also canceled Claim 3 without prejudice or disclaimer. Claim 2 has also been canceled without prejudice or disclaimer. Claim 4 has been further amended to clarify the claim language. Claims 33-34 have been added. Support for Claim 33 can be found throughout the application, particularly on pages 16, 17 and 19. Support for Claim 34 can be found on page 21, lines 3-5.

II. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-7 and 11 are rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph rejections in view of the claim amendments and the following remarks.

The Examiner has rejected claims 1-7 and 11 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claims the subject matter which Applicants regard as the invention. The Examiner does indicate this objection for Claims 1, 2, 7 and 11 can be overcome by identifying the receptor by a Sequence Identification Number. Applicants have included the recitations of Claim 3 into part (b) of Claim 1 to recite SEQ ID NO: 2 which correlates with the cd region of the sigma-1β receptor for humans. Applicants have additionally included a second recitation of

"SEQ ID NO: 2" in section (a) of Claim 11. Accordingly, Applicants submit that Claims 1-2, 4-7 and 11 are not conceding they were indefinite before and are now in condition for allowance.

Additionally, Claim 1 stands rejected as allegedly being indefinite because the stringent conditions of hybridization are not specified. Applicants note that on page 12, lines 19-29, the condition of hybridization of such sequences is noted as they may be carried out under conditions of reduced stringency, medium stringency or even stringent conditions (*e.g.*, conditions represented by a wash stringency of 35-40% Formamide with 5x Denhardt's solution, 0.5% SDS and 1x SSPE at 37°C; conditions represented by a wash stringency of 40-45% Formamide with 5x Denhardt's solution, 0.5% SDS, and 1x SSPE at 42°C; and conditions represented by a wash stringency of 50% Formamide with 5x Denhardt's solution, 0.5% SDS and 1x SSPE at 42°C, respectively) to DNA of SEQ ID NO:1 or SEQ ID NO: 3 disclosed herein in a standard hybridization assay. *See, e.g.*, J. Sambrook et al., *Molecular Cloning, A Laboratory Manual* (2d Ed. 1989) (Cold Spring Harbor Laboratory). Page 12, lines 19-29. Therefore, Applicants submit that such conditions are disclosed within the application. However, in an effort to expedite the allowance of the present application, Applicants have amended Claim 1 to recite polynucleotides comprising "at least 85% percent homology" rather than hybridization conditions. Support for this amendment may be found on page 12, lines 29-32. Accordingly, Applicants respectfully request the rejection of Claim 1 be withdrawn. Additionally, Applicants respectfully request that the rejection to dependent Claims 3-6 be withdrawn.

III. Rejections under 35 U.S.C. § 101

Claims 1-7 and 11 stand rejected under 35 U.S.C. § 101 as allegedly not being supported by a specific and substantial asserted utility or well established utility. Applicants respectfully disagree with this assertion.

This case clearly states an adequate utility consistent with the guidelines set forth in the *Utility Examination Guidelines,* Federal Register 66, 1092 (January 5, 2001). This is not a case where no utility is stated; this is not a case where a vague utility (e.g., "biological activity") is stated; this is not a case where an arguable incredible utility (e.g., treating an intractable disease) is stated; this is not a case where a "throw away" utility is stated. To the contrary, in the present application it is noted that sigma receptors are useful as markers in

the non-invasive detection and visualization of a wide variety of tumors using single photon emission computed tomography and positron emission tomography technology. *See,* page 2, lines 4-6. Furthermore the specification states with regard to the sigma 1B receptor, "[b]ecause this new variant exhibits σ_2-like binding, it is useful in the screening of compounds useful in the detection of the proliferation state of tumors, as well as in other uses. The new $\sigma_{1\beta}$ variant finds particular use in the non-invasive diagnosis of cancer and more particularly in the diagnosis of proliferative cancer cells." Page 5, lines 10-14. Page 6, lines 8-13 notes that the compounds of the present application allows for such uses as diagnostic compounds for the imagining of tumor cells. These compounds also are useful as therapeutics for the treatment of cancer and other disorders of cell proliferation. These ligand compounds of the present application are also useful in methods of determining the proliferative status of a tumor. *See,* page 6, lines 8-13. Furthermore, the methods and compositions of the present invention are also useful in relation to non-cancer disorders of cell proliferation. These diseases include, but are not limited to, benign tumors, hyperplasias, hyperpigmentation of the skin, psoriasis, and any other disorder wherein cell proliferation is uncontrolled, and control, diagnosis, or imaging of such proliferation is desired. *See,* page 10, lines 17-22. Applicants also note that the $\sigma_{1\beta}$ receptor exhibits σ_2-like binding, as described in experimental detail below. As such, methods for determining the proliferative state of a cell by determining the cell's ability to bind σ_2 receptors may now be carried out using a cell's ability to bind $\sigma_{1\beta}$. *See*, pages 34-35, lines 32-33 and 1-2. Applicants further note that these methods for determining the proliferative status of cancer cells are carried out by determining the ability of proliferative cells to bind σ_1 and $\sigma_{1\beta}$ ligands, respectively. The ratio of $\sigma_{1\beta}$ to σ_1 density on a cell is an indicator of the proliferative state of the cell. Applicants further note that σ receptors have been defined as nonopiate, nondopaminergic, and nonphencyclidine receptors based on their ligand binding characteristics. *See, e.g.*, Thomas, *Life Sci.* 46:1279-1286 (1990); Bem, et al., *Cancer Res.* 51: 6558-6562 (1991); John, et al., *J. Nucl. Med.* 37:267P (1996); John, et al., , *J. Nuc. Med.* 34:2169-2175 (1993); John, et al., *J. Med. Chem.* 37:1737-1739 (1994); John, et al., *Life Sci.* 56:2385-2392 (1995); John, et al., *J. Nucl. Med.* 37:205P (1996). Thus, the utilities of the present invention are specific, substantial, and credible, and clearly satisfy the requirements of 35 U.S.C. § 101. This case is nothing like *Brenner v. Manson,* cited by the Examiner, where little or no utility

of any kind was stated for the compounds made by the claim process. Hence, it is respectfully submitted that this rejection should be withdrawn.

IV. Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-7 and 11 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse these rejections due to the amendments to the claims and the reasons enumerated both above in the response to the 35 U.S.C. § 101 rejections and enumerated below.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Applicants note that they have amended Claims 1 and 11 to recite specific structurally related sequences which encode for a Φ_{13} receptor whose functionality and biological activity has been disclosed throughout the specification. Furthermore, these amendments remove the hybridization issues by including sequence homology language and the inactivated variant issue raised by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1, 4-7 and 11.

V. Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 1, 2, 5-7 and 11 also stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not containing subject matter described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully disagree with this assertion for the reasons enumerated in the previous sections and for the reasons discussed below.

Applicants note that the United States Patent and Trademark Office has provided guidelines regarding the policy objectives of the written description requirement. The

guidelines explain that the policy goals are to i) clearly convey to the public what was invented; ii) put in possession of what the applicant claims as the invention; and iii) prevent an applicant from claiming subject matter that was not described in the specification as filed. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1104-05 (Jan. 5, 2001). Applicants note that the specification discloses that SEQ ID NO:1 is the human mRNA (cDNA) sequence of $\sigma_{1\beta}$, and SEQ ID NO:2 is the human $\sigma_{1\beta}$ amino acid sequence. Therefore, the structure of the invention has been clearly established and one of skill in the art could readily predict the structure as claimed. Applicants have additionally amended Claim 1 to recite that the polynucleotides comprising SEQ ID NO: 1 or that encode SEQ ID NO: 2 are at least 85% similar to SEQ ID NO: 1 or SEQ ID NO: 2 and encode a $\Phi_{1\exists}$ receptor. Applicants further note that it may be advantageous to produce nucleotide sequences encoding $\sigma_{1\beta}$ or its derivatives possessing a substantially different codon usage. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding $\sigma_{1\beta}$ and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence. Applicants further submit that for the reasons discussed above, there is clear evidence of activity of a $\Phi_{1\exists}$ receptor. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejections.

Additionally, Applicants note that the United States Patent and Trademark Office has clarified the standard for examining applications for compliance with respect to the written description requirement of 35 U.S.C. §112, first paragraph. These guidelines state, in part:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed . . .. Consequently, rejection of an original claim for lack of written description should be rare.

66 Fed. Reg. 1099, 1105 (Jan. 5, 2001) (emphasis added). Applicants respectfully contend that the specification does provide a sufficient written description so that one skilled in the art would appreciate that the Applicant was in possession of the claimed invention at the time of filing. polynucleotide Applicants submit that a person of skill in the art can readily envision polynucleotides comprising SEQ ID NO. 1, encoding SEQ ID NO.2 or active fragments thereof. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph to Claims 1, 5-7 and 11.

CONCLUSION

In view of the amendments and remarks presented herein, Applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact Applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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Clara R. Beard